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3101 Burnet Ave

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Human Papillomavirus

Presented by

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University of Cincinnati College of Medicine



Etiologic Agents

- Family: Papillomaviridae
 - Genus: Polyomavirus
 - Mice
 - Monkey SV40 – Vacuolating Agent
 - Man – BK Virus, GU Tract,
 - Renal Transplant Patients, JC Virus,
Leucoencephalopathy
 - Genus: Papillomavirus
 - Human, Bovine, Rabbit, Deer, Horse, Dog, Monkey



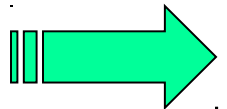
The Clinical Problem



The Viruses Prevalence

The Wart Problem

- 100 + Types
- The most common viral sexually transmitted disease
- Between 50% and 75% of the sexually active population is infected





Prevalence

- In the population at large
 - 1% present with lesion
 - 2-5% of PAP tests
 - 10% have HPT-DNA by Southern blot
 - 40-50% have HPV-DNA by PCR*
 - 2000 – Estimation:
 - 75% of sexually active population is infected

*JAMA, 265:472, 1991



Role of HPV-DNA in Malignant Onchogenesis

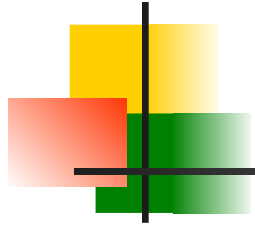
- Patients with HPV 16-18 have a rapid progression to C.I.N. And invasion
- HPV-DNA found in 90+% of genital cancers
 - 60% type 16
 - 18% type 18
 - 20% other
 - 2% negative



Transmission

Infected human exfoliated cells

- External genitalia / male and female
- Urethra
- Cervix and vagina
- Anus and rectum
- Mouth
- Trachea
- Lung
- Skin
- Fomites
- Infected body fluids



Zonotic PV

Animal Tumor

Associated Tumor Type

Rabbit (Shope) Papilloma
Carcinoma

Squamous Cell

Bovine Papilloma

Squamous Cell Carcinoma

Deer Sarcoma Fibrosarcoma

Human (Wart) Papilloma Squamous Cell
Carcinoma



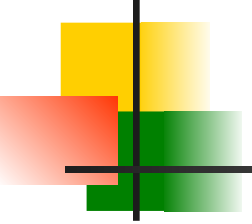
Spectrum of HPV Disease

<u>HPV Type</u>	<u>Primary Source/Lesion</u>
1	Plantar warts
2, 4, 27, 29, 40	Verruca vulgaris
3, 10, 26, 28, 41	Flat warts
3, 5, 8, 9, 12, 14, 15, 17, 19-25, 36, 47, 50	Epidermodysplasia verruciformis



Spectrum of HPV Disease

<u>HPV Type</u>	<u>Primary Source/Lesion</u>
16, 18, 30, 31, 33, 35, 39, 42-45, 51, 52, 56	Cervical dysplasia, carcinoma; laryngeal carcinoma
6, 11	Buschke-Lowenstein tumors (verrucous carcinomas) condylomata acuminata
5,10, 16, 18, 34, 31,37, 39, 42, 55	Bowenoid papulosis

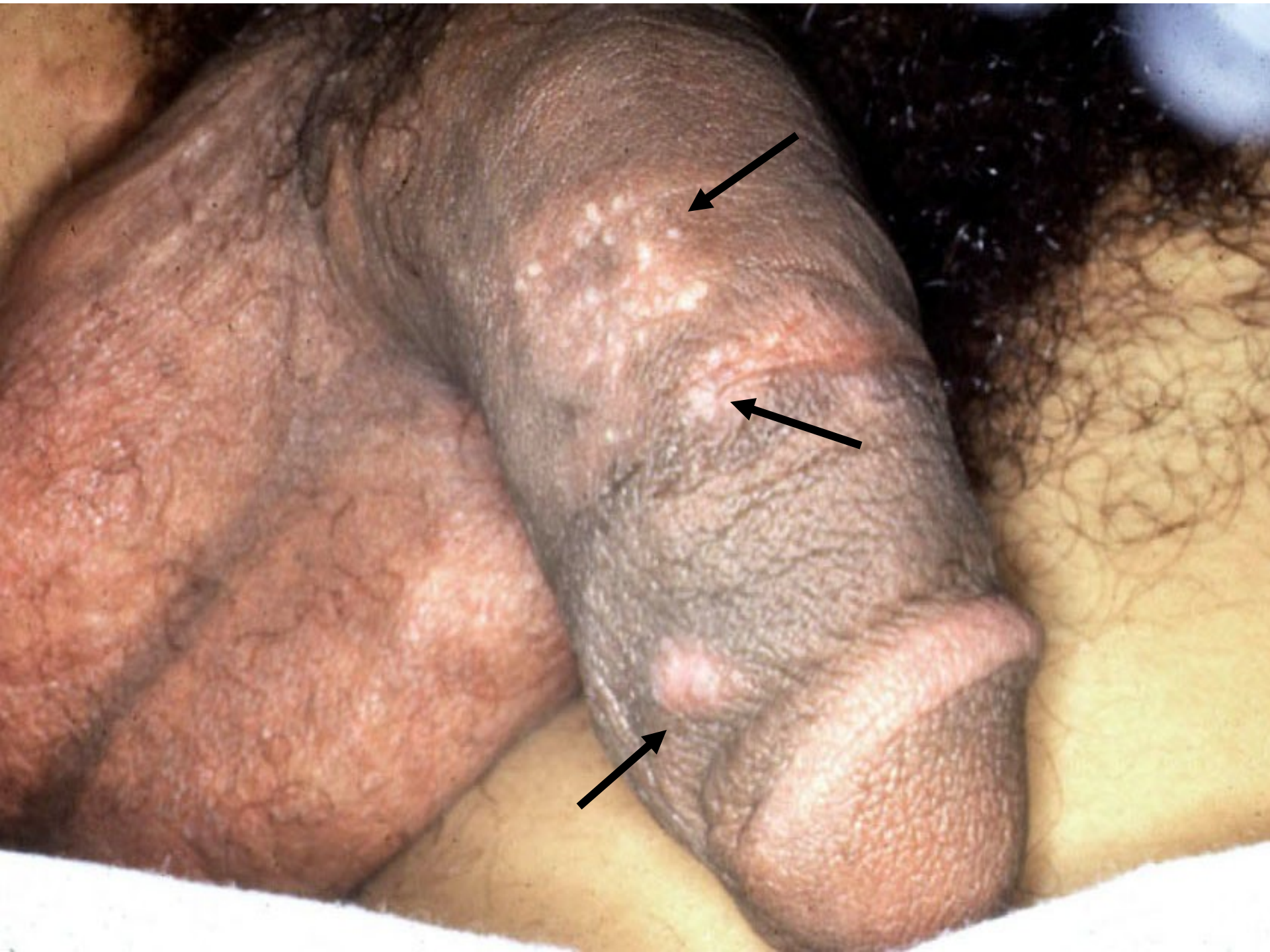


HPV Incidence of Genital Subclinical Papilloma Virus Infection (SPI)

- 50% of males exposed to contacts with clinical disease have SPI.
 - 100% infected.
- Clinical male bladder and proximal urethral lesions rare *unless* there is hematuria, perimeatal, and/or urethral wart.



Genital Warts Male



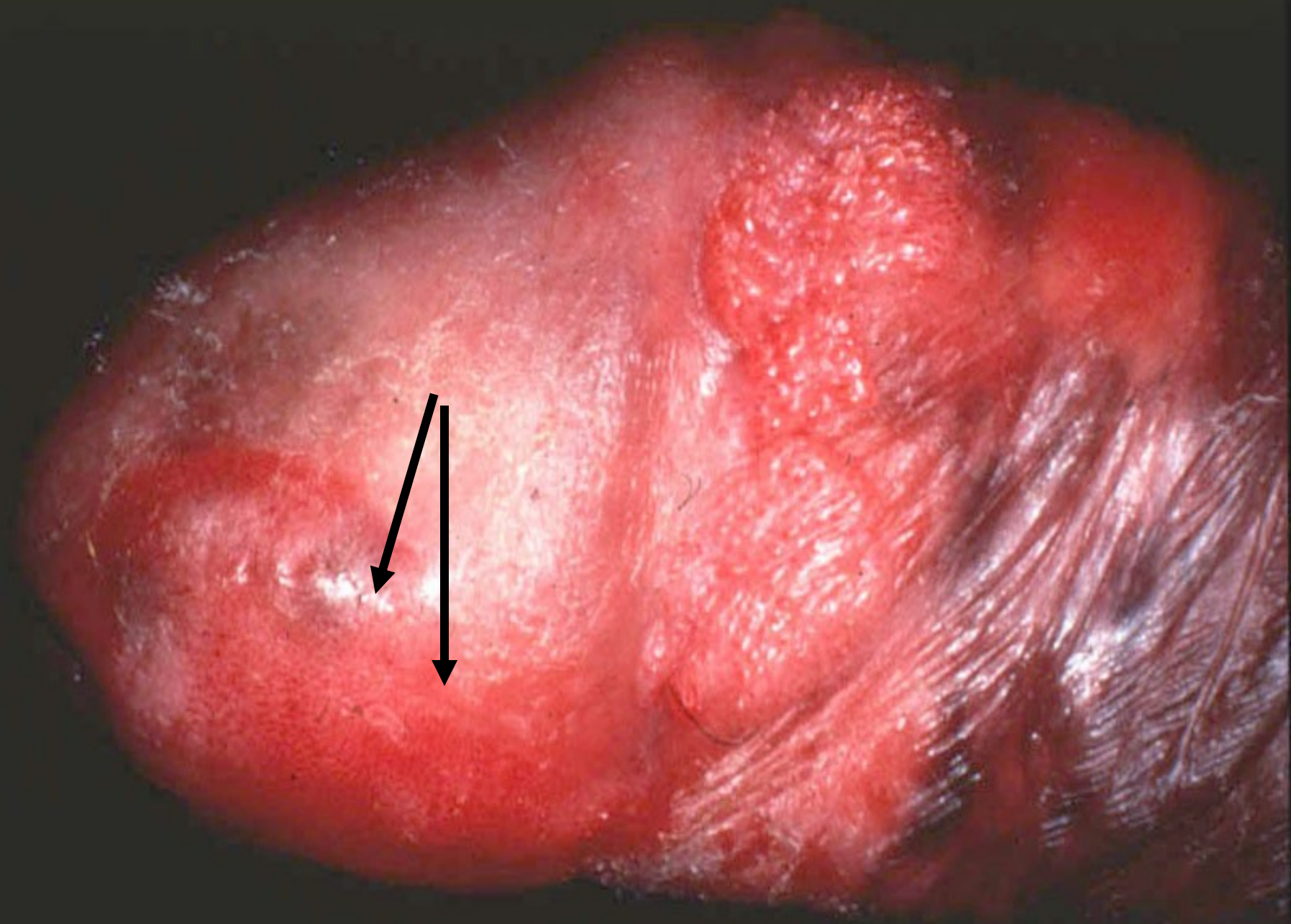


Warts -Urethral Vestibule





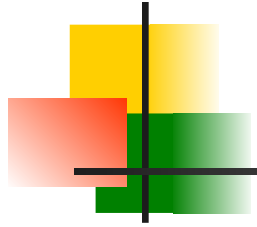




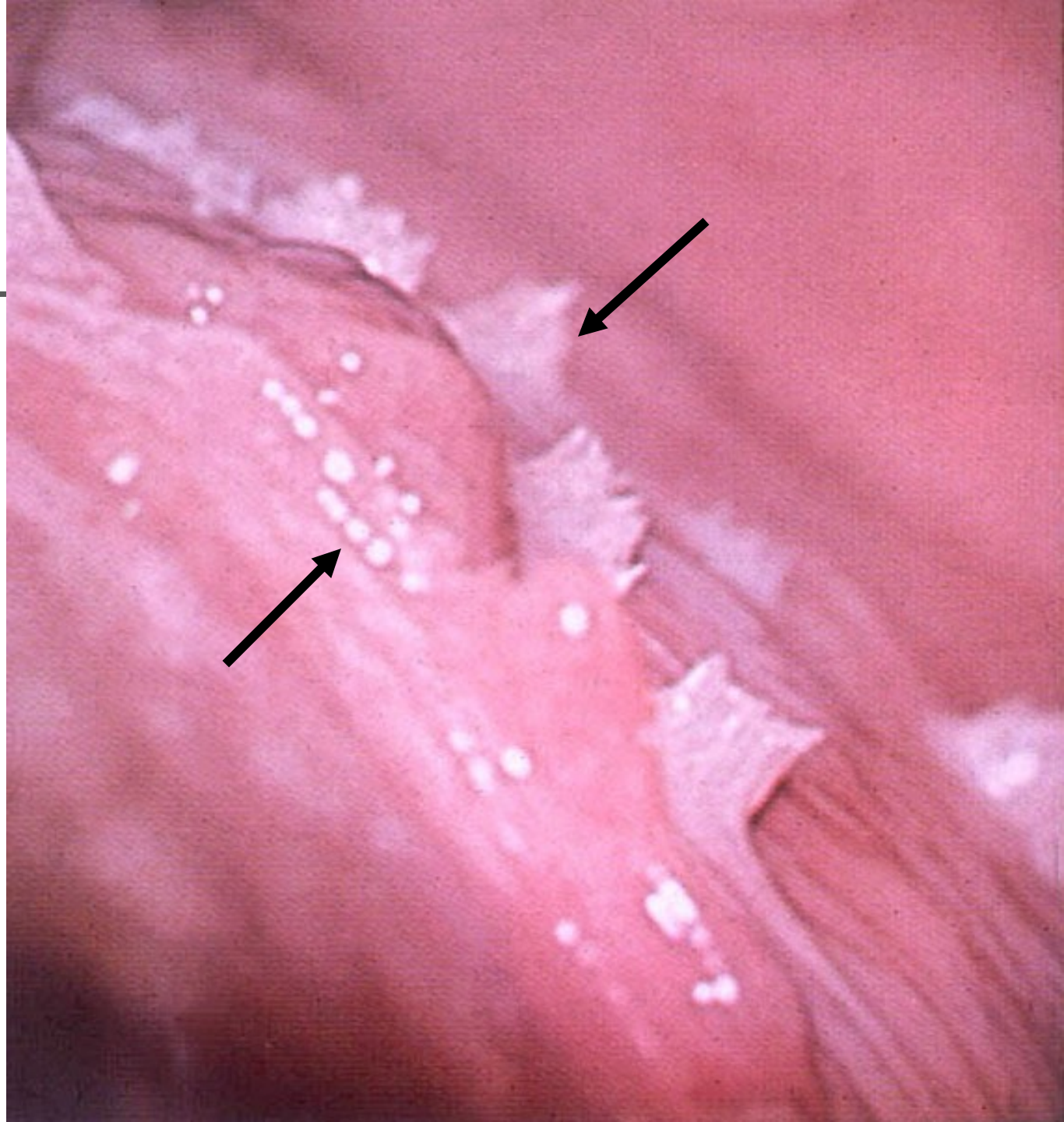


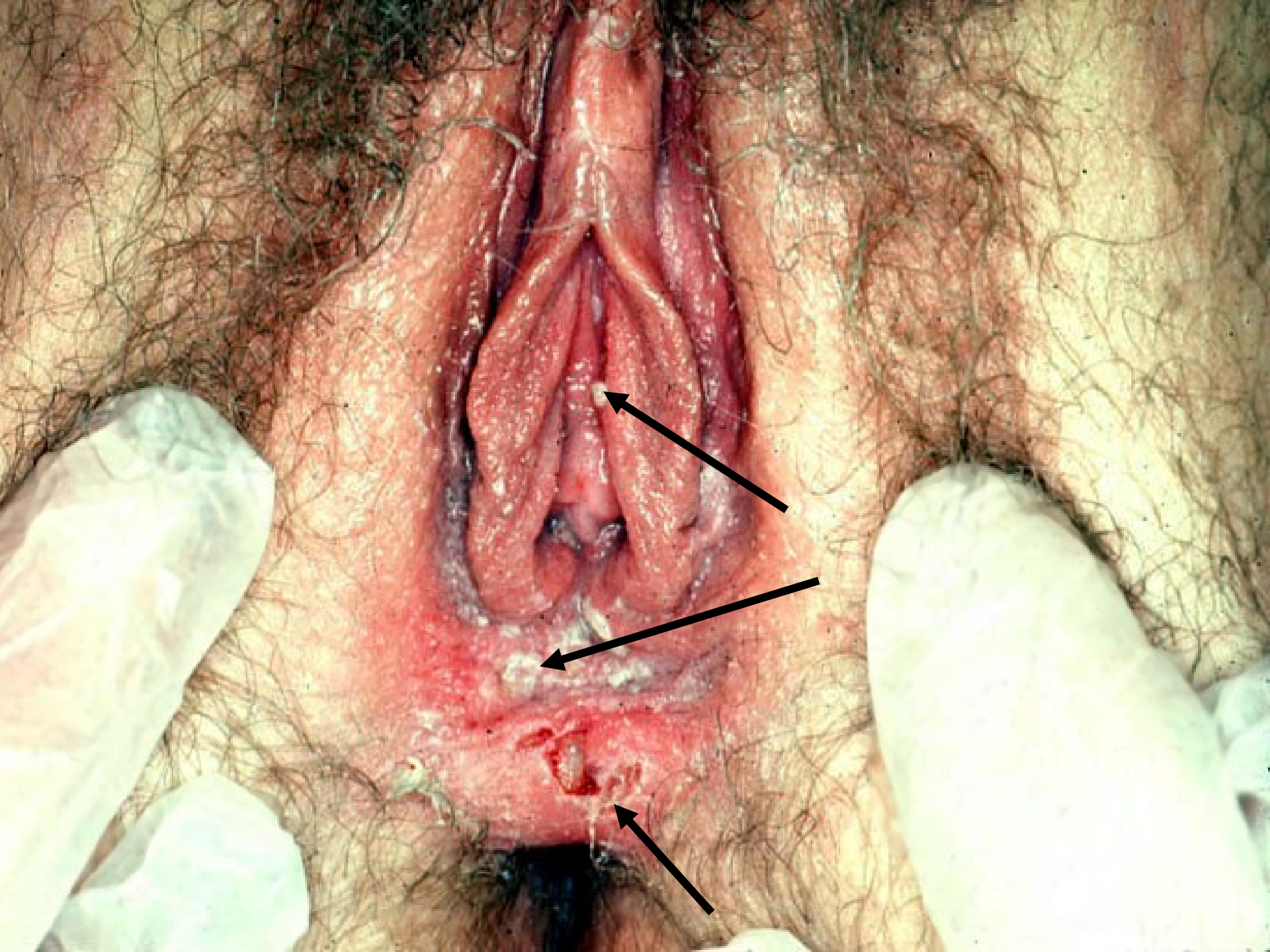


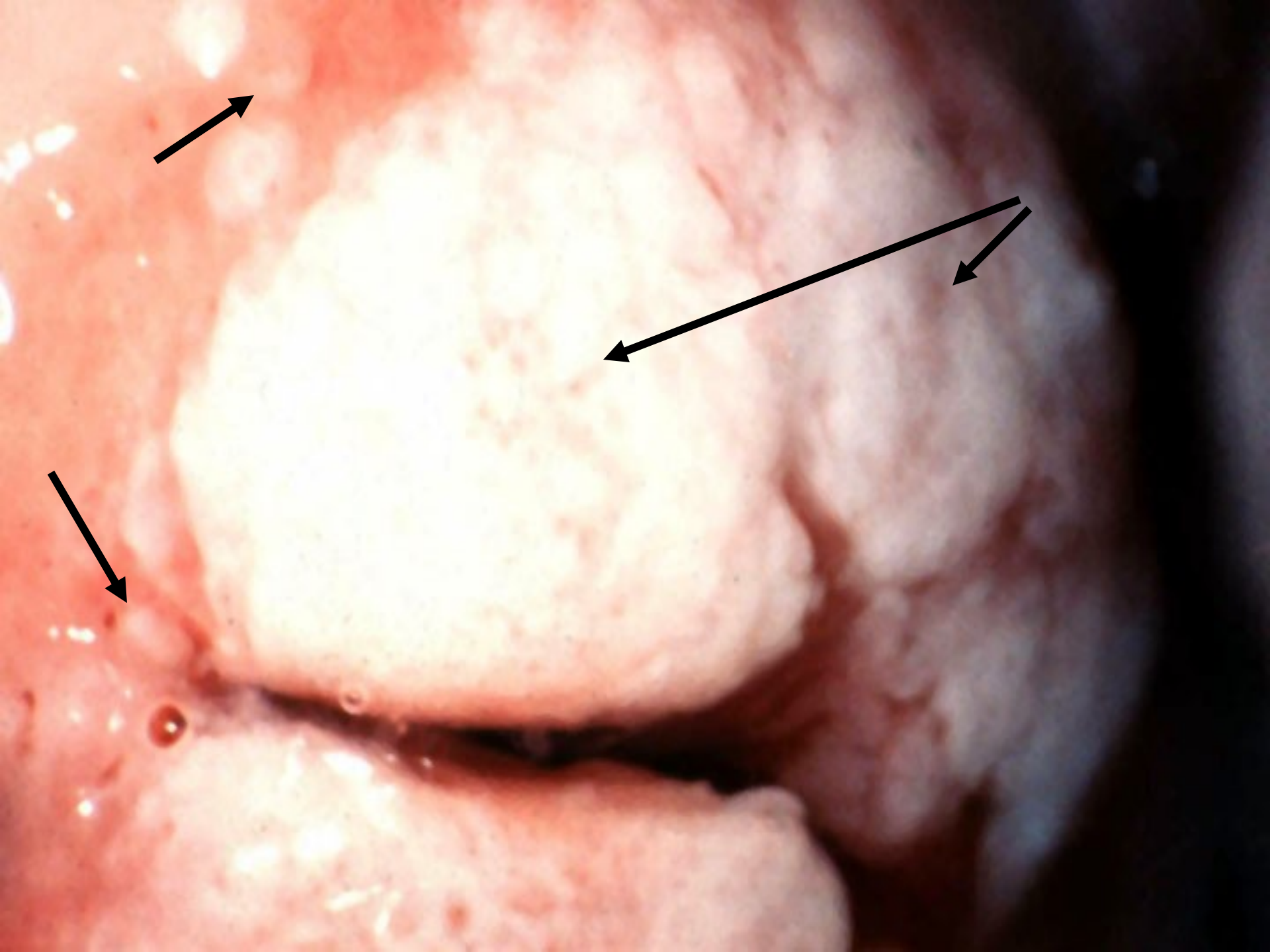
Genital Wart Female



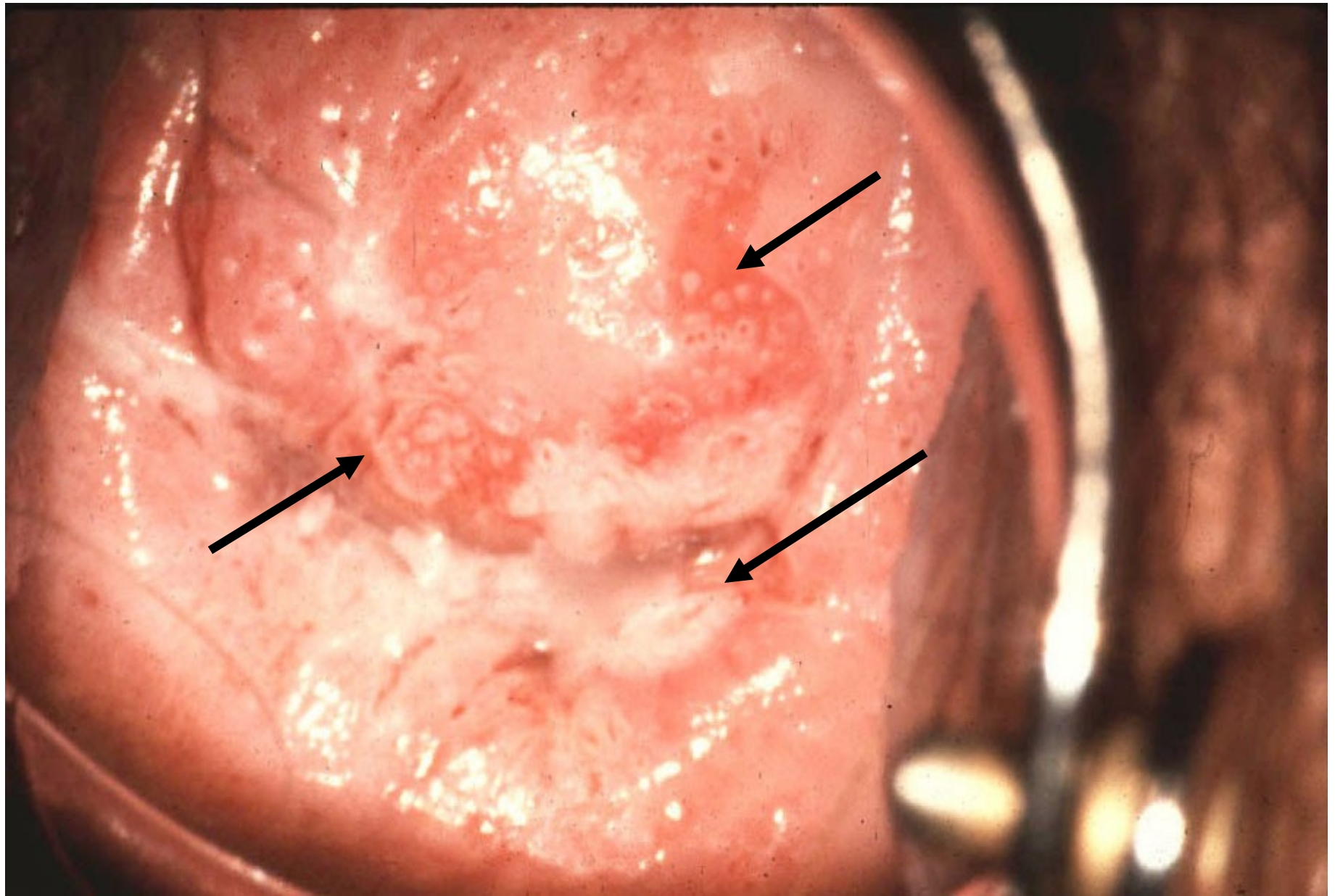
GENITAL:
Spiked
Vaginal
Condylom
a











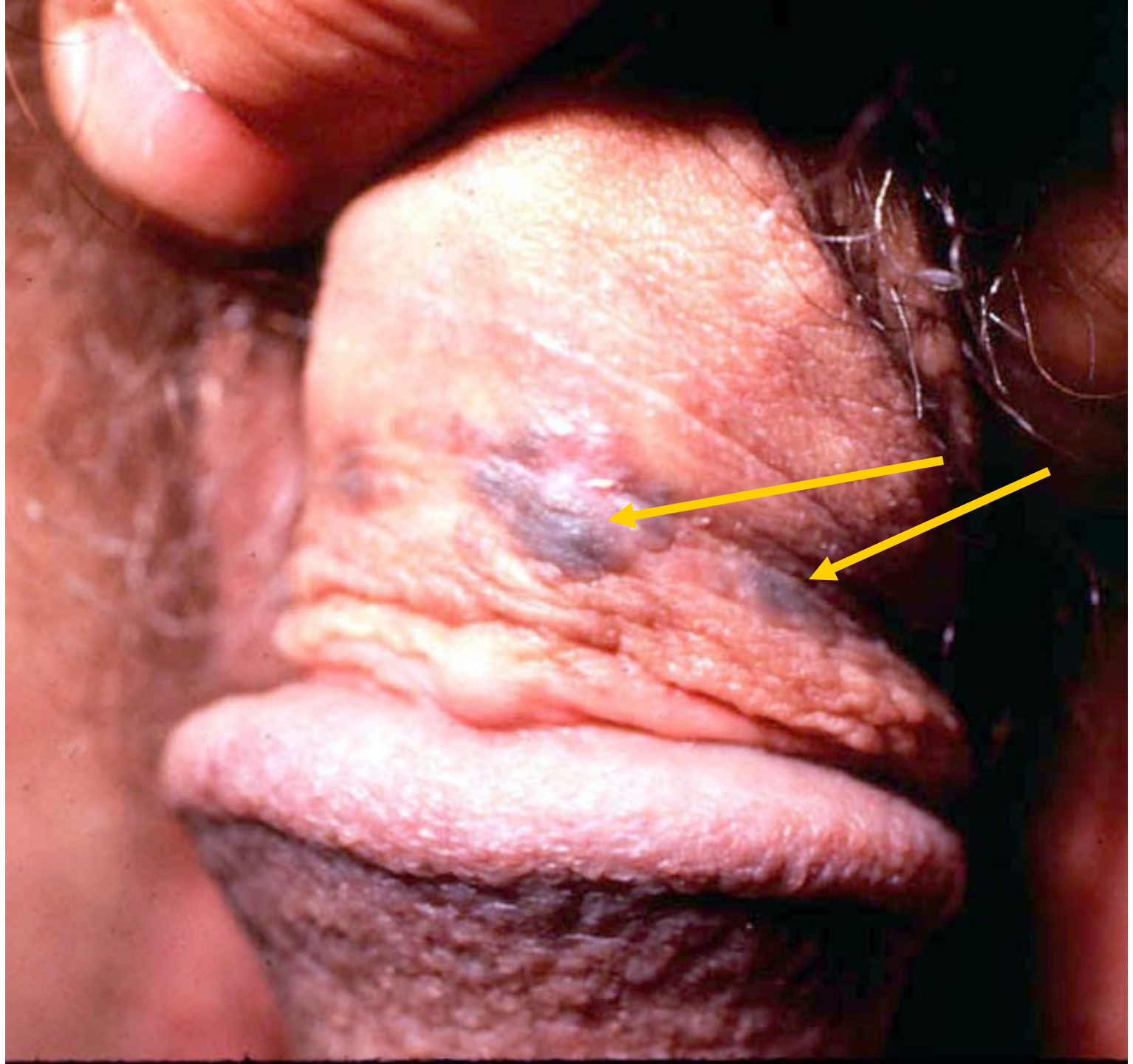


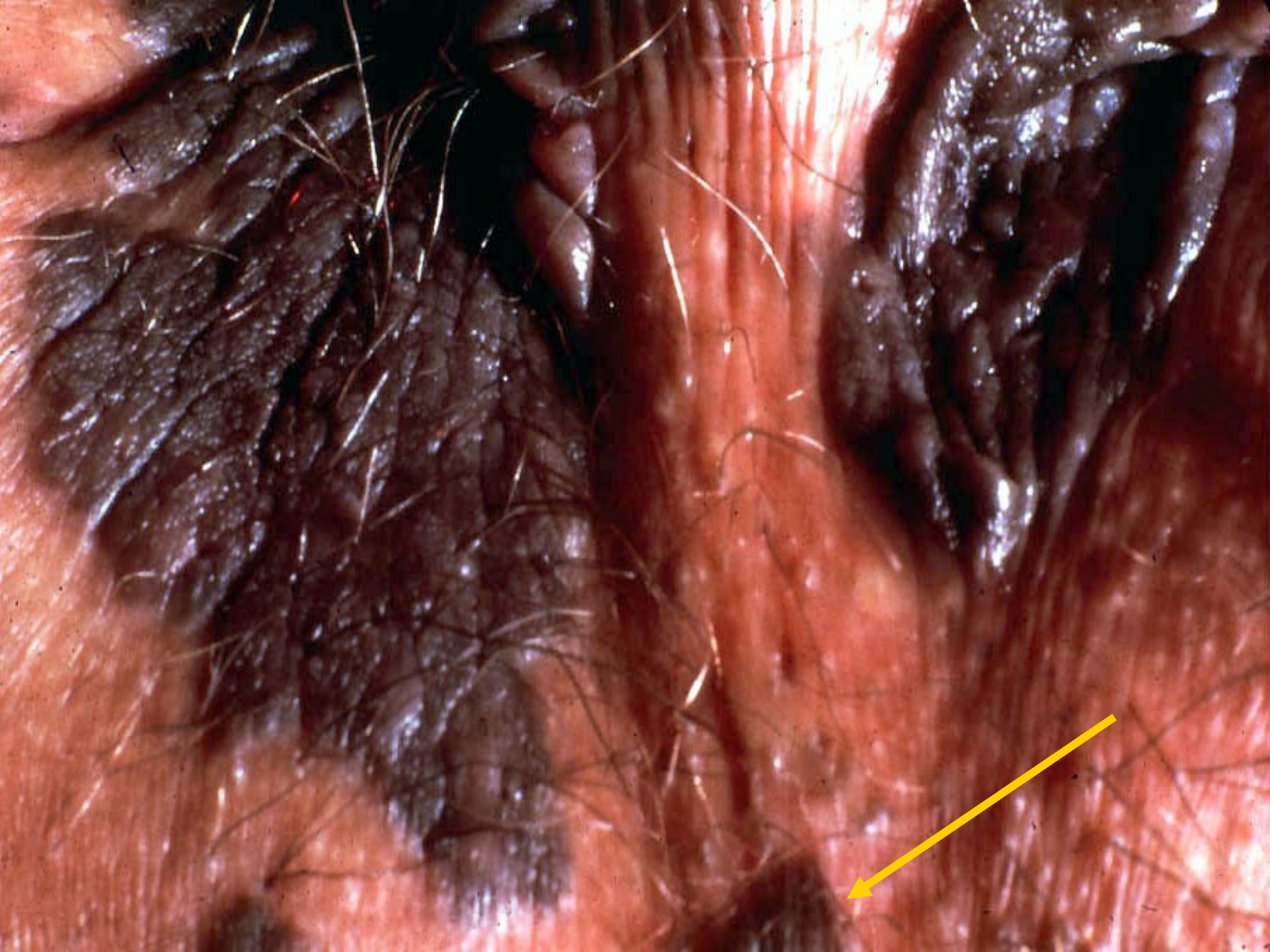
Bowenoid Papulosis

HPV's

- 5, 10
- 16, 18, 31
- 34, 37, 39, 42, 55

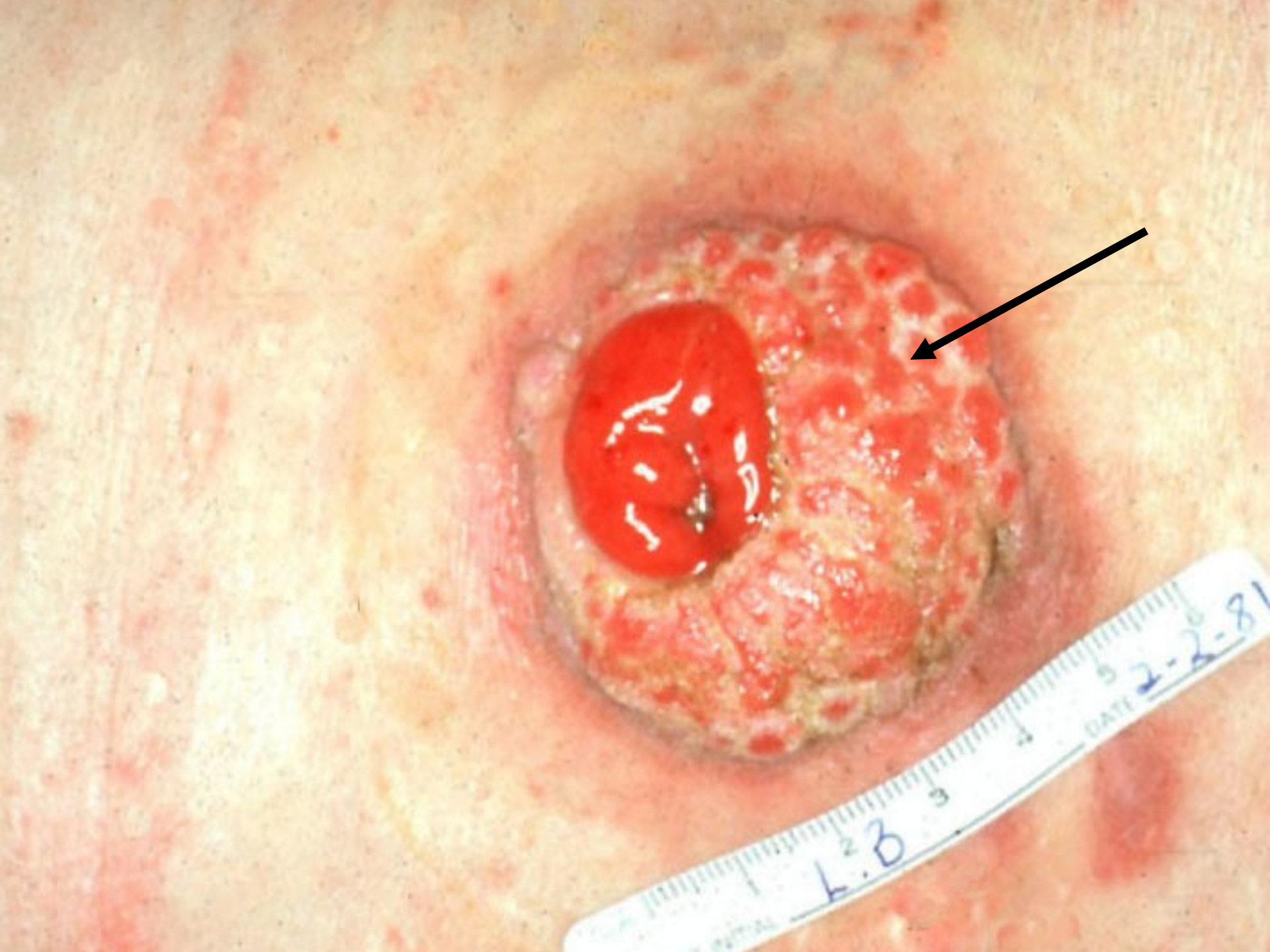








Gastrointestinal and Anal Warts: HPV Types









Oral and Respiratory Warts

☐ 1, 3

☐ 6, 11

☐ 16, 18

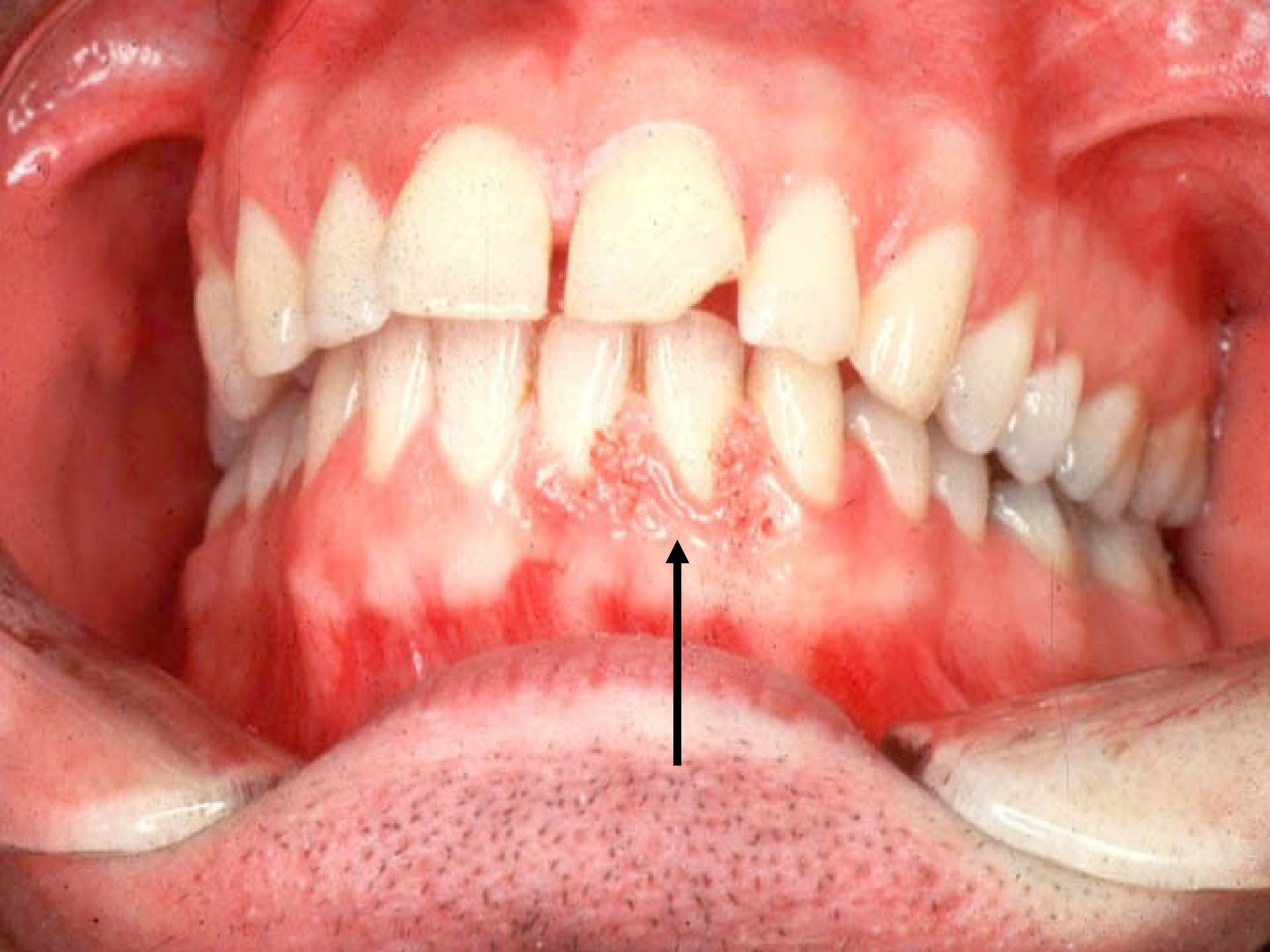
☐ other

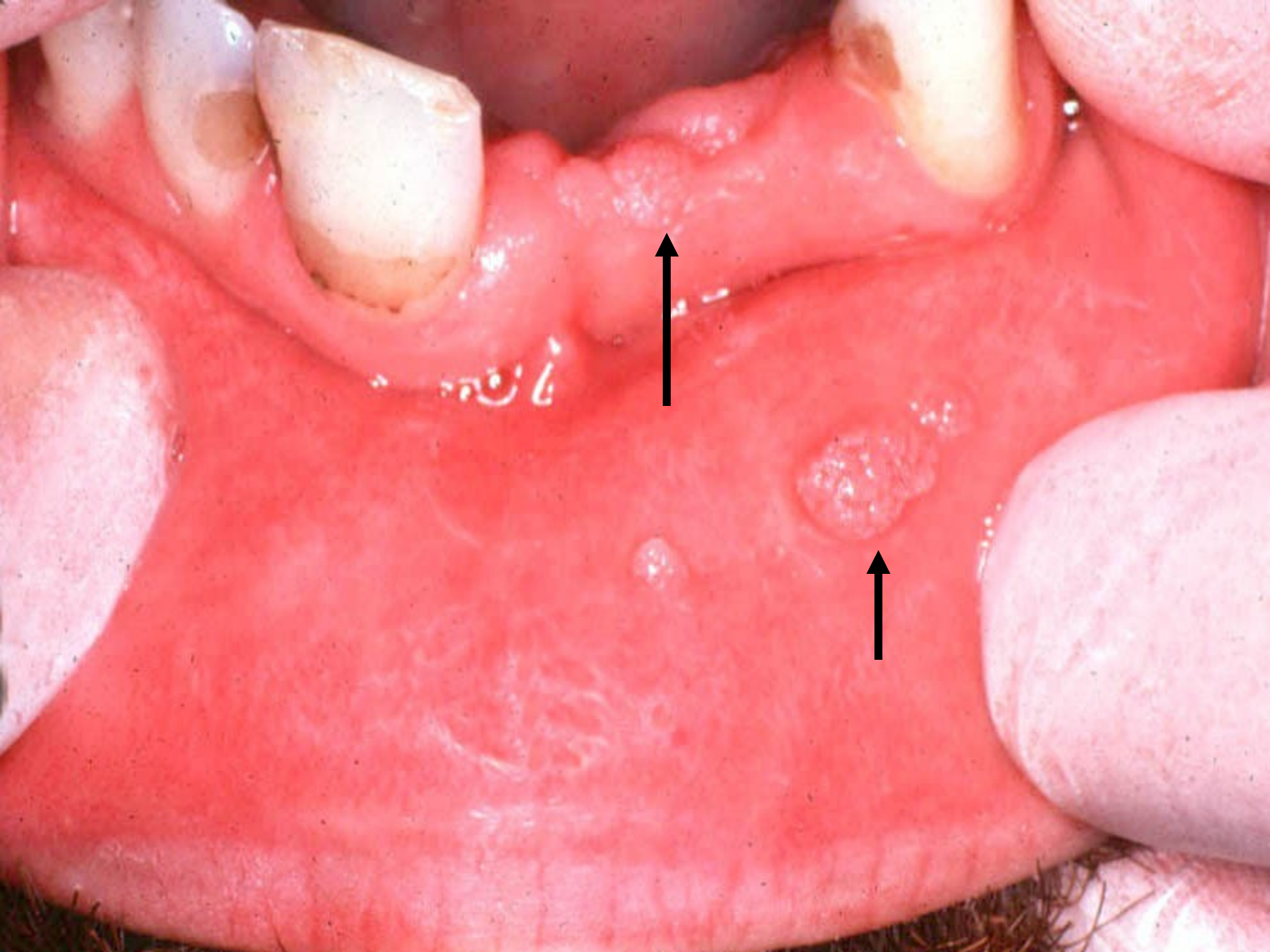


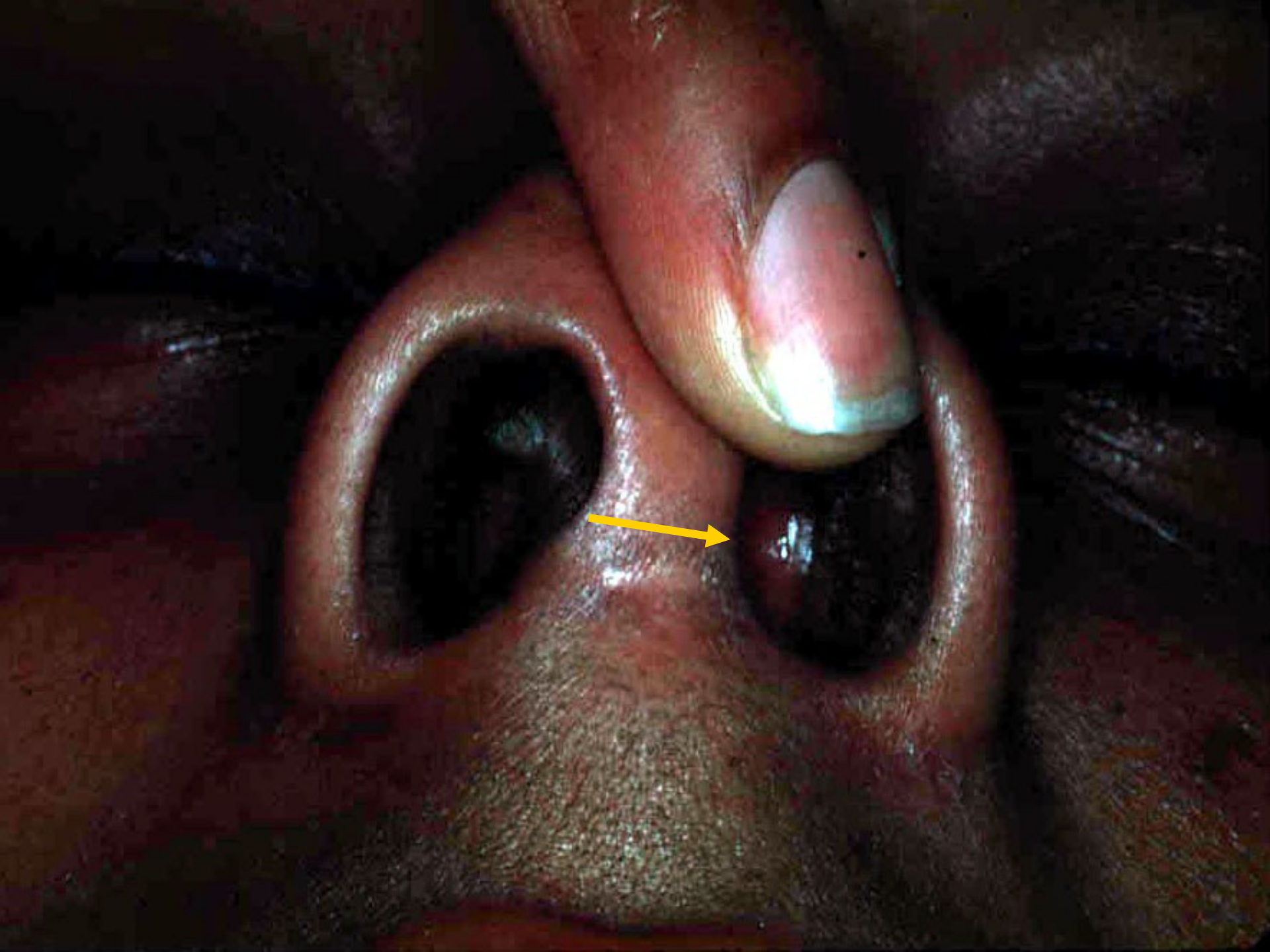
HPV Incidence

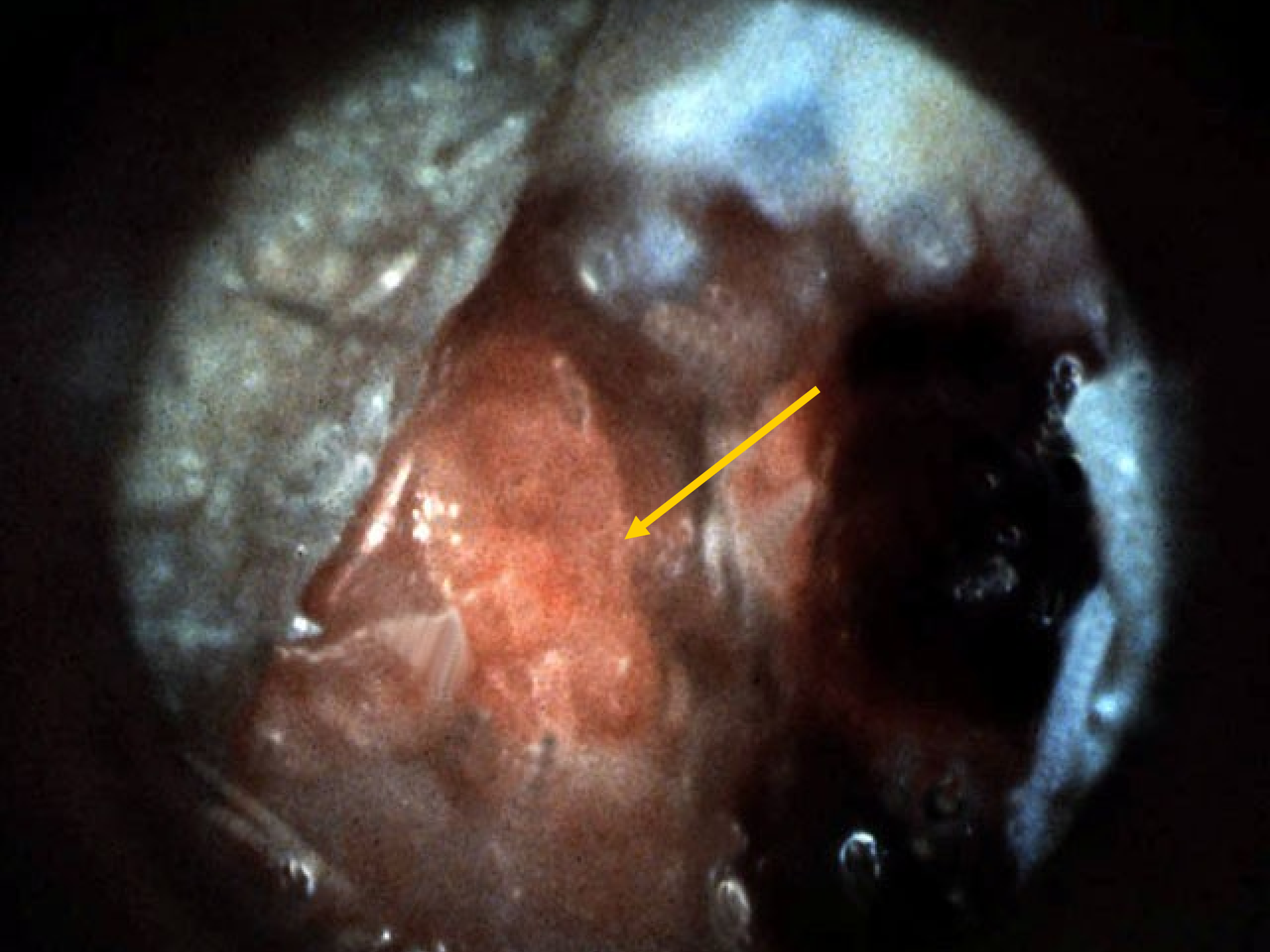
Clinically Apparent Disease In the Oral Cavity, Nasopharynx, Larynx, Trachea, and Lung

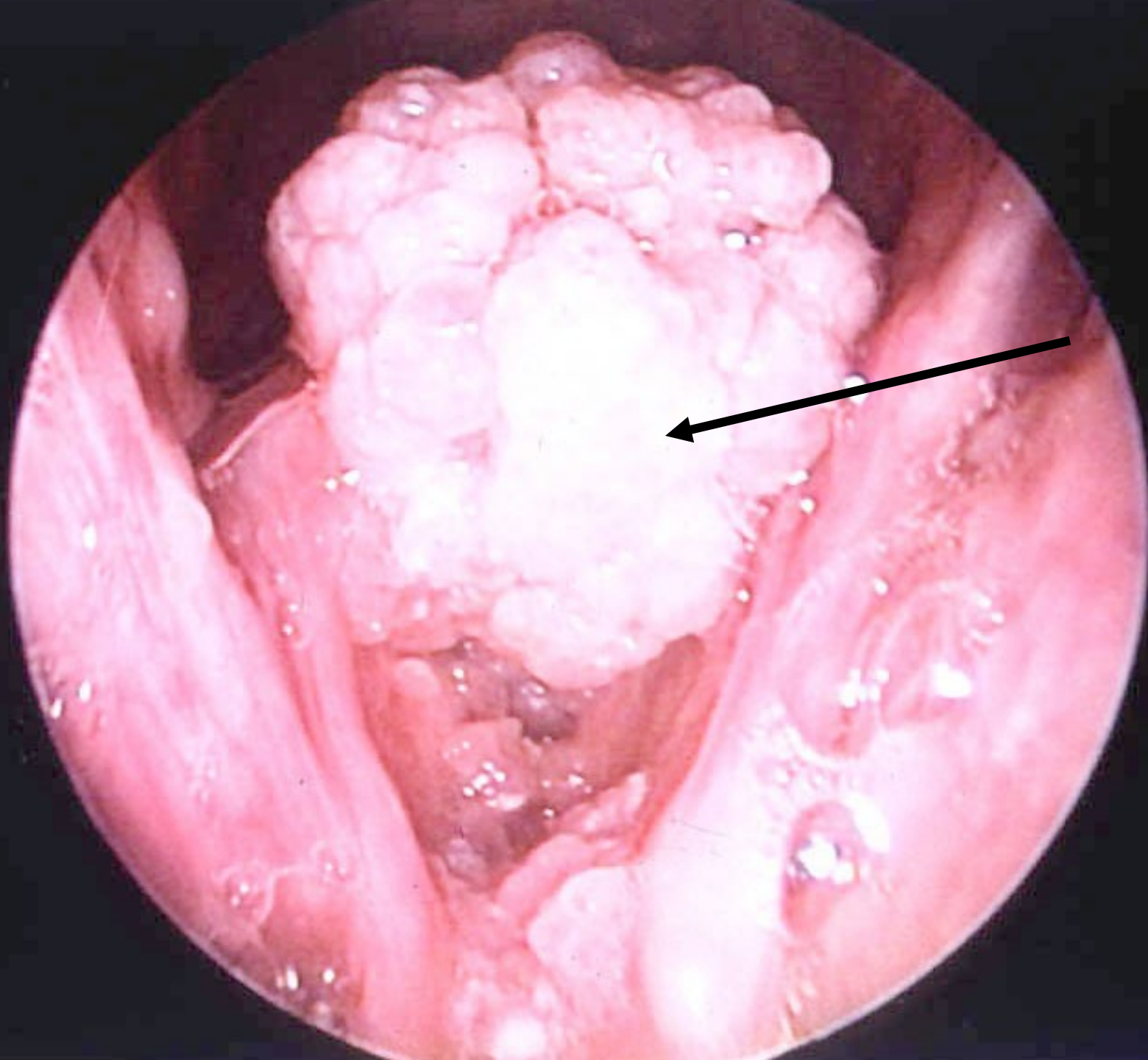
- 50% of cases are adult onset!
- Precise incidence is unknown (esp. SPI)
- Age range – infancy through old age
- Children Peak 2 - 5 Years

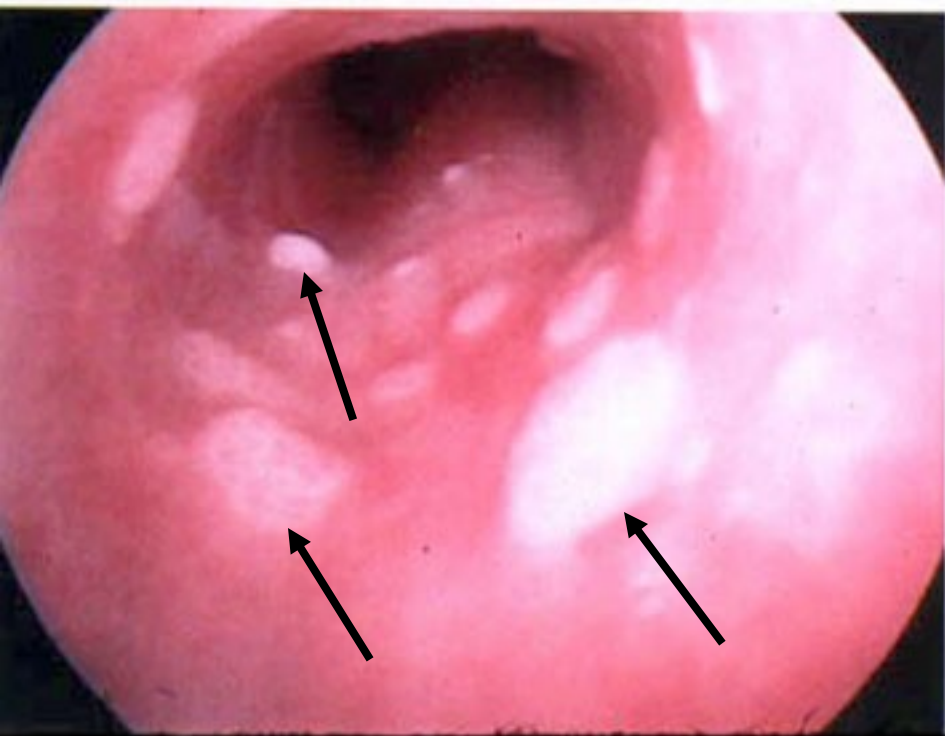














Children and Warts

- Genital 1, 2, 4, 6, 11, 16, 18
- Oral 1, 3, 4, 6, 11, 34
- Nasopharyngeal 6, 11, 16, 18
- Cutaneous 1, 2, 3, 4, 5 most common









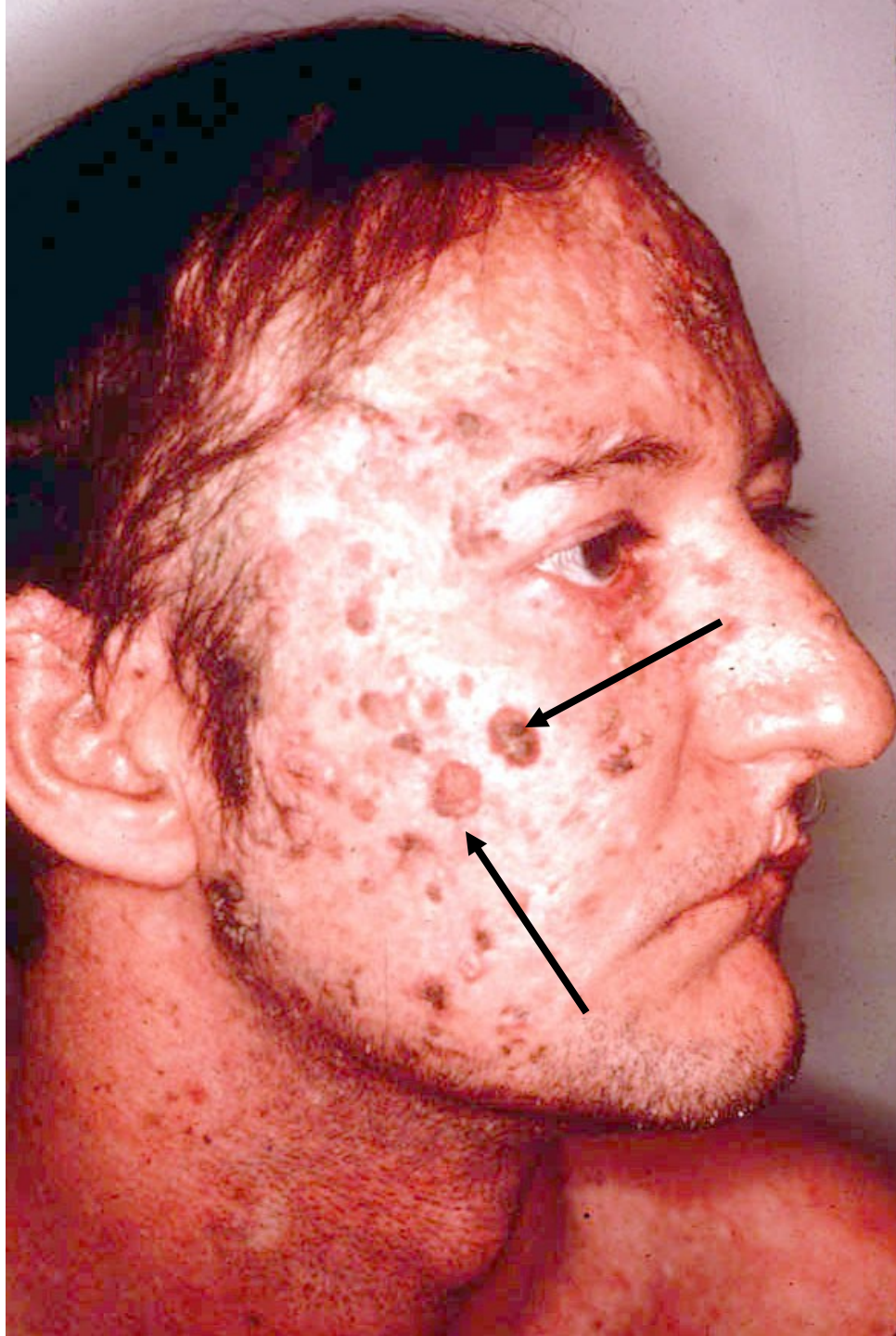
Cutaneous Warts

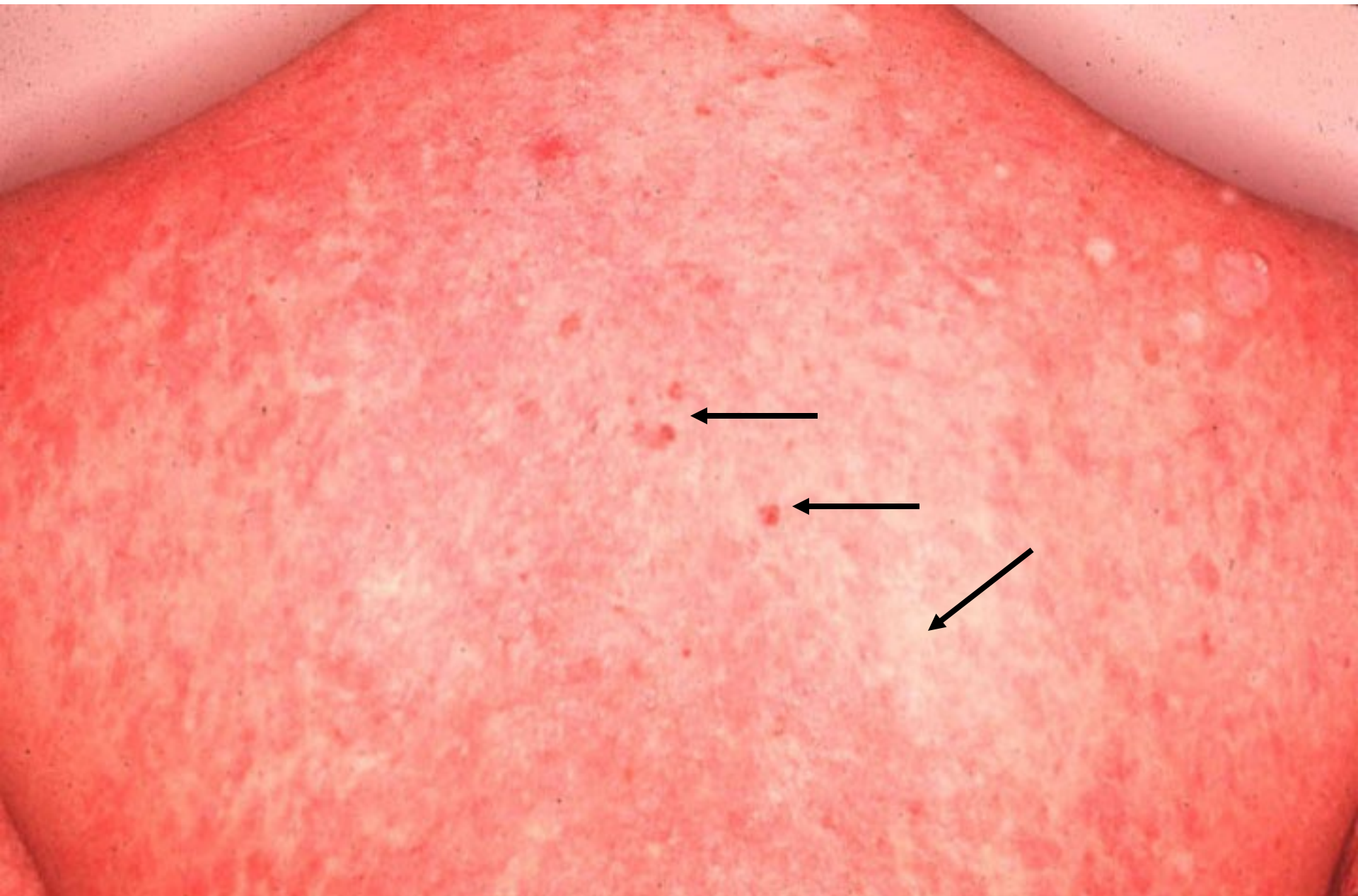


Cutaneous Warts

- Most Important in Cutaneous Disease
- Common - 1, 2, 3, 4
- Epidermal Dysplasia Verruciformis (E.V.)
- Malignant - 3, 5, 8, 14











HPV and Cancer



Cervical Cancer

- Second most common cancer in women – HPV 16-18-31 in some developing countries not US (~9th)
- In U.S., 9,710 new cervical cancer cases per year and 3,700 deaths
- Most common and fatal cancer in developing countries
 - 1st/2nd most commonly dx'd cancer in women ~ 50% mortality rate



Therapy - HPV

Treatment Rationale for External Genital Warts (EGWs)



- Cosmetic considerations
- Psychosocial
- Reduce virus load
- Restore (or improve) normal function
- Relieve symptoms



Criteria for the Selection of Wart Therapy

- Immune status of the patient
 - Age
 - Disease
 - Drugs
 - Pregnancy
- Extent of clinical tumor
- Location of clinical tumor
- Response to prior therapies
- Pregnancy



Therapeutic Objectives

- Decrease tumor burden
- Increase cellular immune response
- Normalize rate and quality of cell proliferation
- Control viral spread



Therapeutic Objectives

- Decrease tumor burden
 - Destroy infected cells
 - Debulk the tumor
- Increase cellular immune response
 - Activate helper T-cells
 - Rhus, oidiomycin
 - Mumps vaccine
 - Squaric acid / D.N.C.B. / Etc.
 - Interferons



Therapeutic Objectives (cont.)

- Normalize rate and quality of cell proliferation
 - Vitamin A
 - Accutane / Etretinate
 - Bleomycin
 - 5-FU
 - I.D.U.
- Control viral spread
 - Counseling
 - Barriers

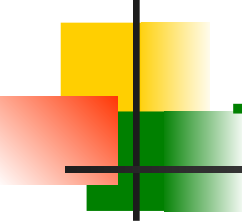
Traditional Therapy for Anogenital Warts

Modality	Response	Recovery
Excision	100%	60%
Electrocautery & curettage	100%	9%
Laser therapy	66-95%	1-14%
Cryosurgery	42-88%	7-40%
Trichloroacetic Acid	60-85%	40%
Phodophyllin	22-98%	50%
Podophyllotoxin (Podofilox)	36-60%	33%
5- Fluorouracil	33-70%	100%



Other Common Treatments

- Bleomycin - intralesionally
- Rhus with occlusion
- Oral and Topical Retinoids
- Interferon intralesionally
- Imiquimod
- Combinations



Immunotherapy and Other Therapy for Anogenital Warts

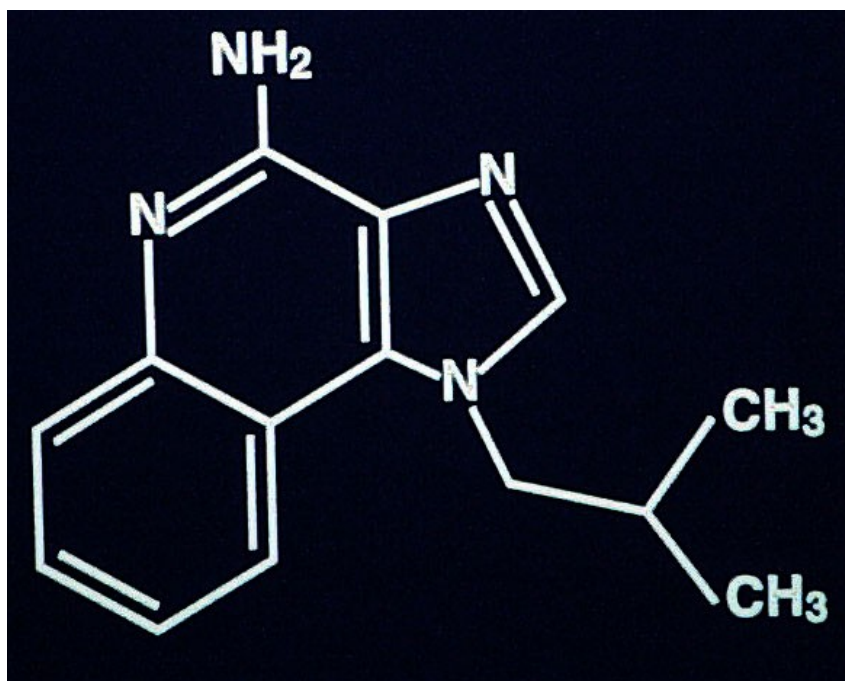
■ Immunotherapy

- Autogenous wart vaccine
- BCG vaccine
- Interferon
- Other lymphokines

■ Other Therapy

- Hypnosis

Imiquimod (R-837, S-3608)



1-(2-methylpropyl)-
1H-imidazo-[4,5-C]
quinolin-4-amine

Interferon inducer
Immune-response
modifer



Imiquimod Response

- Self-administered topical 4% cream
- Application: 3x / week for \leq 16 week
- Clearance rates (intent-to-treat)

	<u>Imiquimod</u>	<u>Vehicle</u>
■ All	50%	11%
■ Female	72%	20%
■ Male	33%	5%



HPV Vaccines

Jessica Kahn, MD MPH

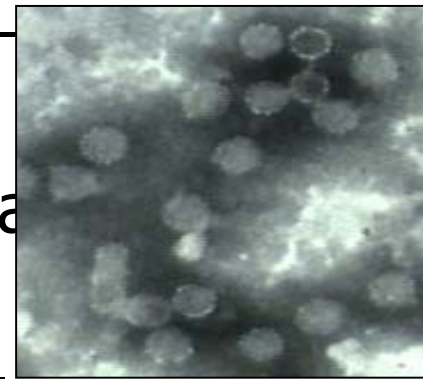
Associate Professor of Pediatrics
Cincinnati Children's Hospital Medical Center



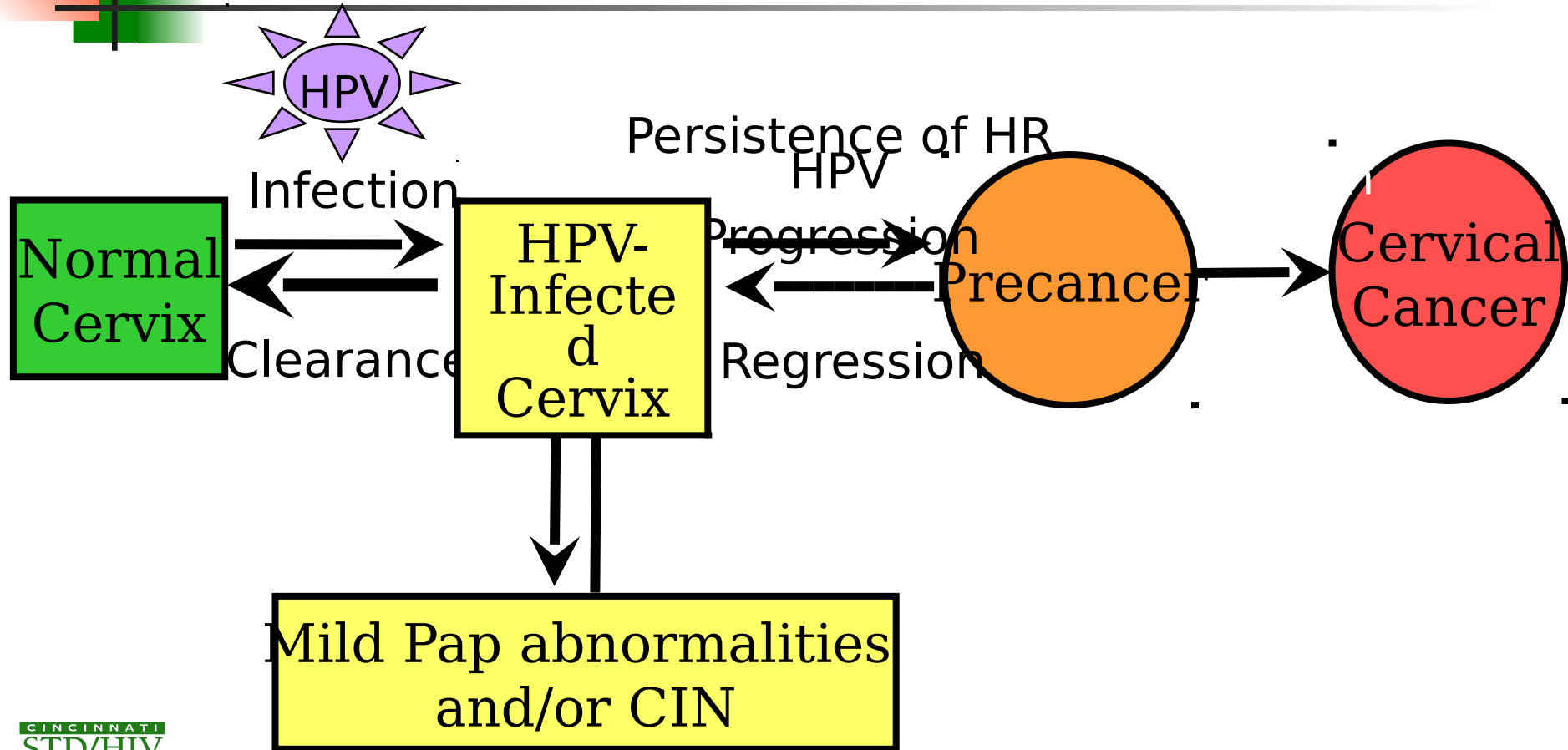
University of Cincinnati College of Medicine

HPV Vaccines

- Prophylactic (prevent HPV infection) vs. therapeutic (treat HPV-related disease)
- Prophylactic vaccines: virus-like particles (VLPs)
 - Recombinant viral capsids - identical to HPV virions morphologically, but no viral DNA core
 - Induce virus-neutralizing Ab response, but pose no infectious or oncogenic risk

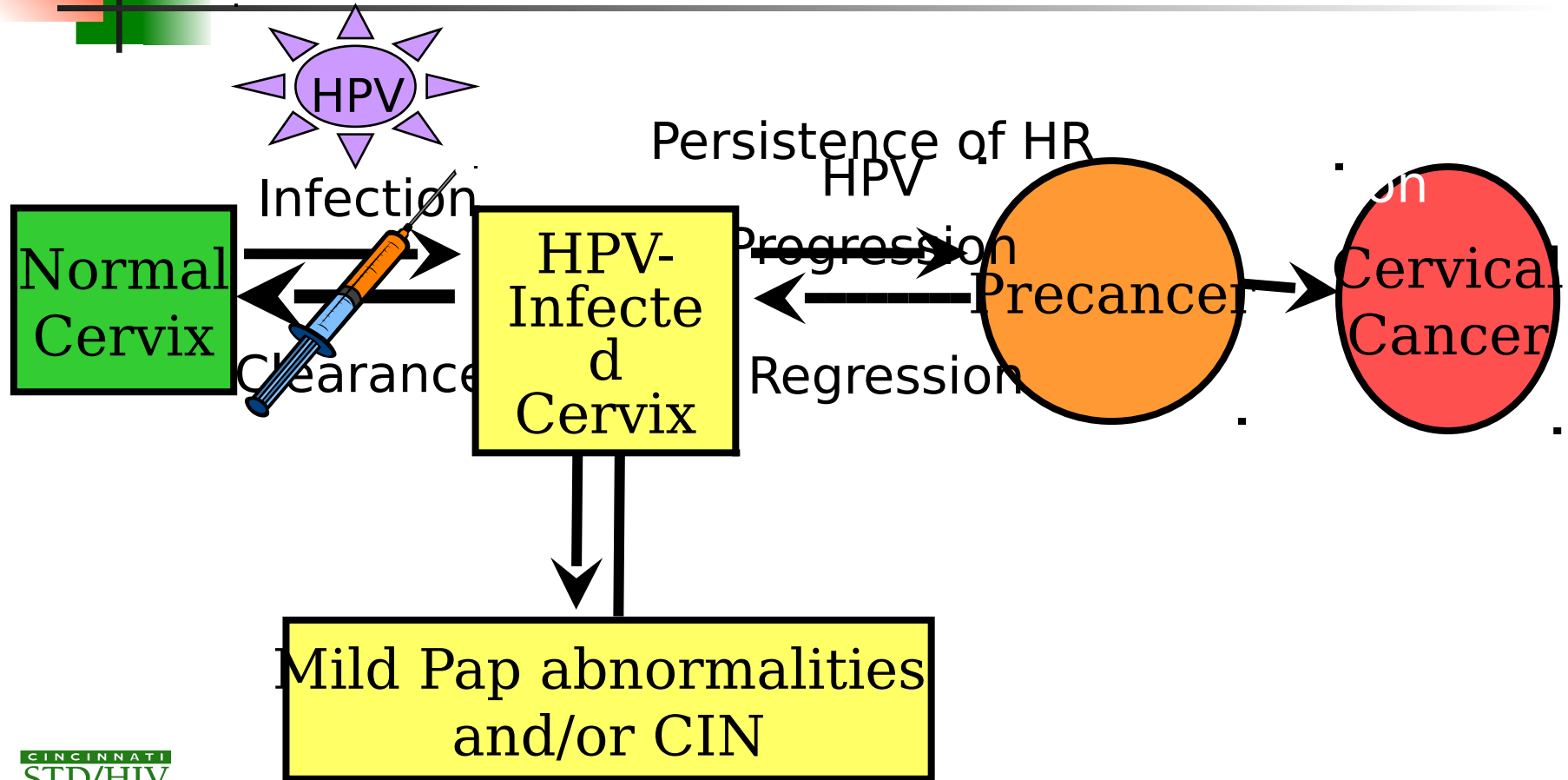


Cervical Carcinogenesis



Schiffman, Kjaer. *J Natl Cancer Inst Monogr.* 2

Vaccines Prevent Infection

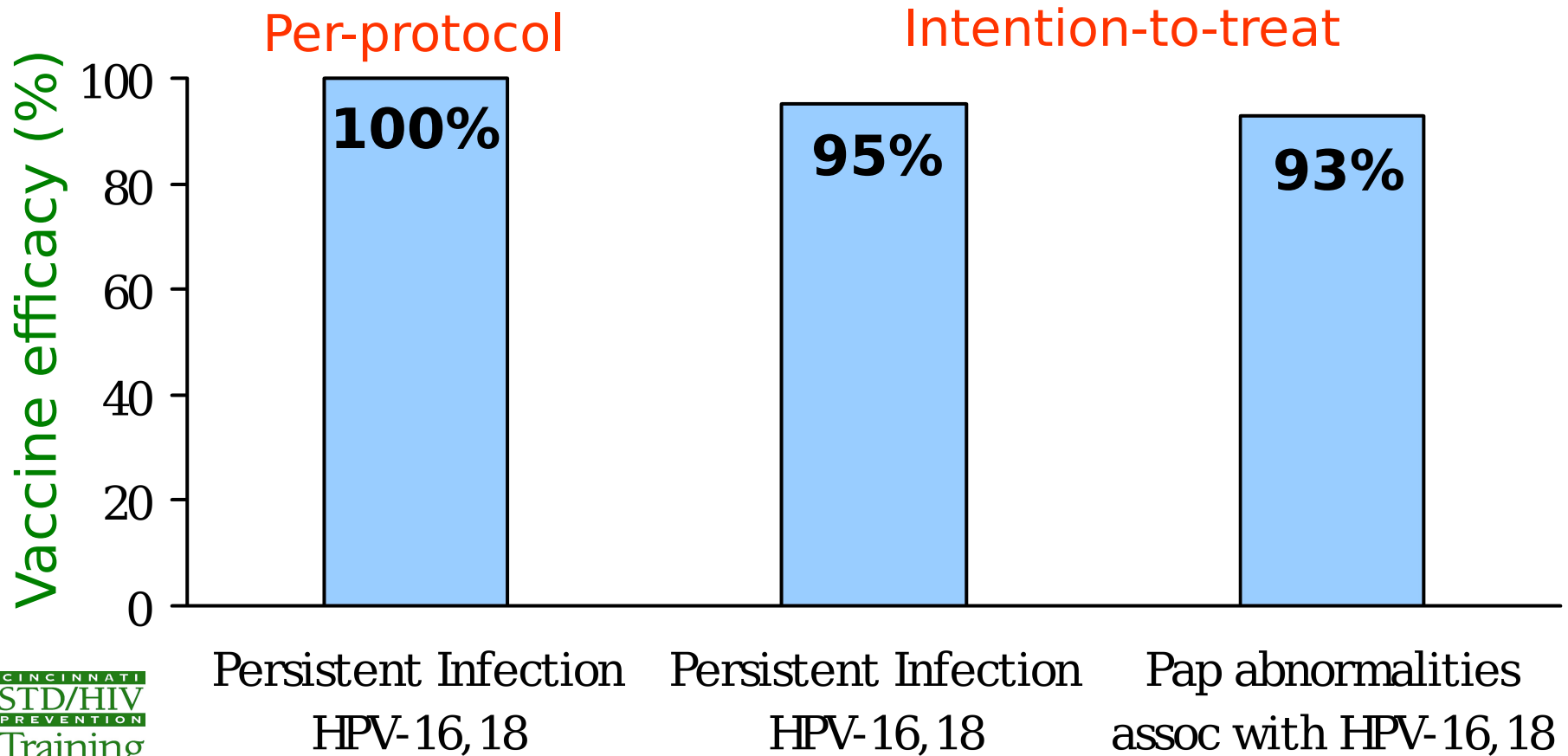




HPV Vaccines in Large Clinical Trials

- HPV-16,18 (Cervarix, GlaxoSmithKline)
 - Designed to prevent cervical cancer, other malignancies
- HPV-6,11,16,18 (Gardasil, Merck)
 - Designed to prevent cervical cancer and other malignancies, genital warts, RRP
 - Efficacy evaluated in 4 placebo-controlled, double-blind, randomized Phase II and III clinical studies of 20,541 women 16-26 yrs

HPV-16,18 Vaccine Trial (N=1,113 women, 15-25 years)





HPV-16,18 Vaccine: Safety

Serious adverse events	Vaccine (%)	Placebo (%)
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Related to vaccination	0	0
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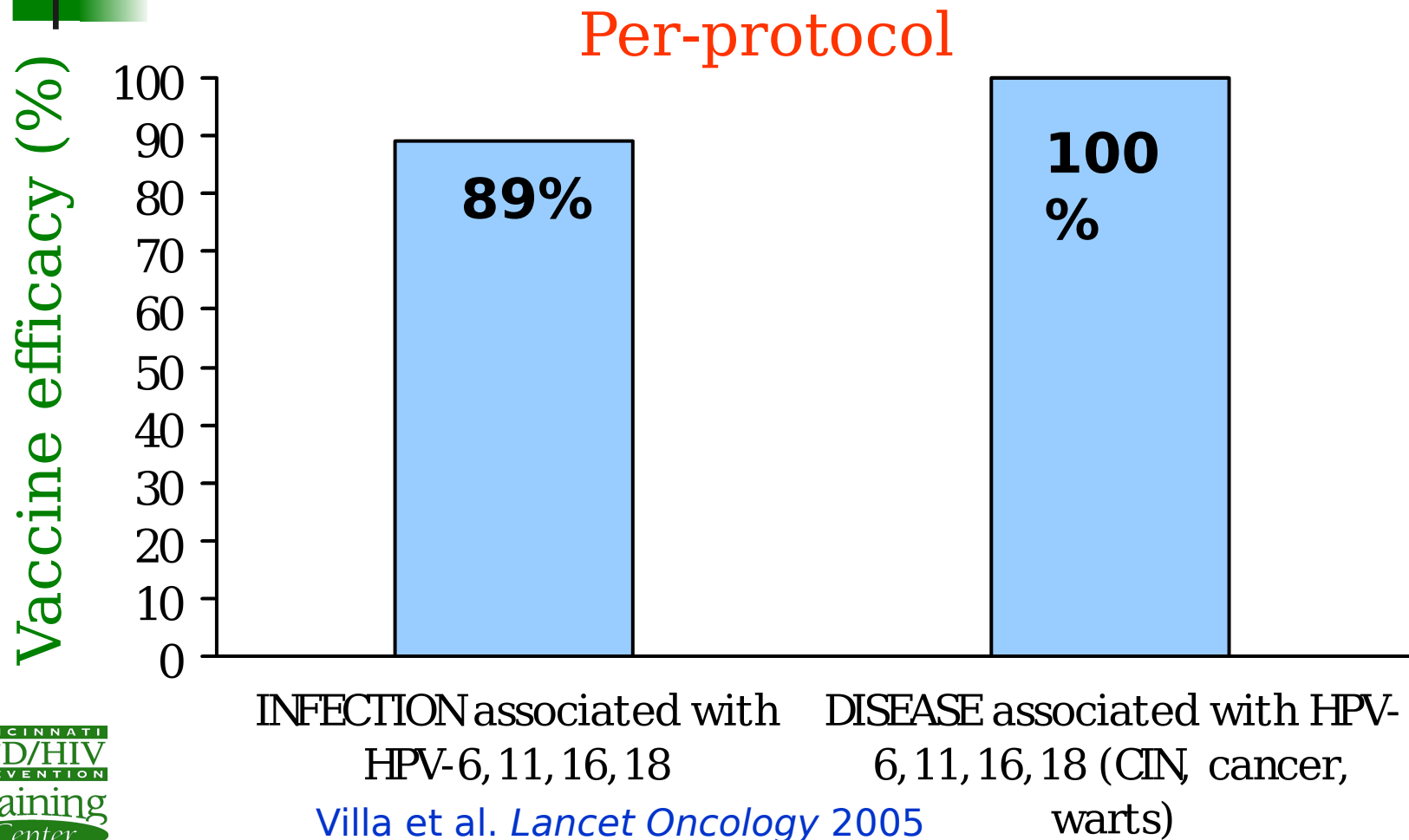
Common symptoms	Vaccine (%)	Placebo (%)
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Pain	93	87
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Redness	34	21
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Swelling	36	24
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HPV-6,11,16,18 Vaccine Trial (N=522, 16-23 years)



HPV-6,11,16,18 Vaccine: Safety

Serious Adverse Events	Vaccine (%)	Placebo (%)
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Related to vaccination	0	0
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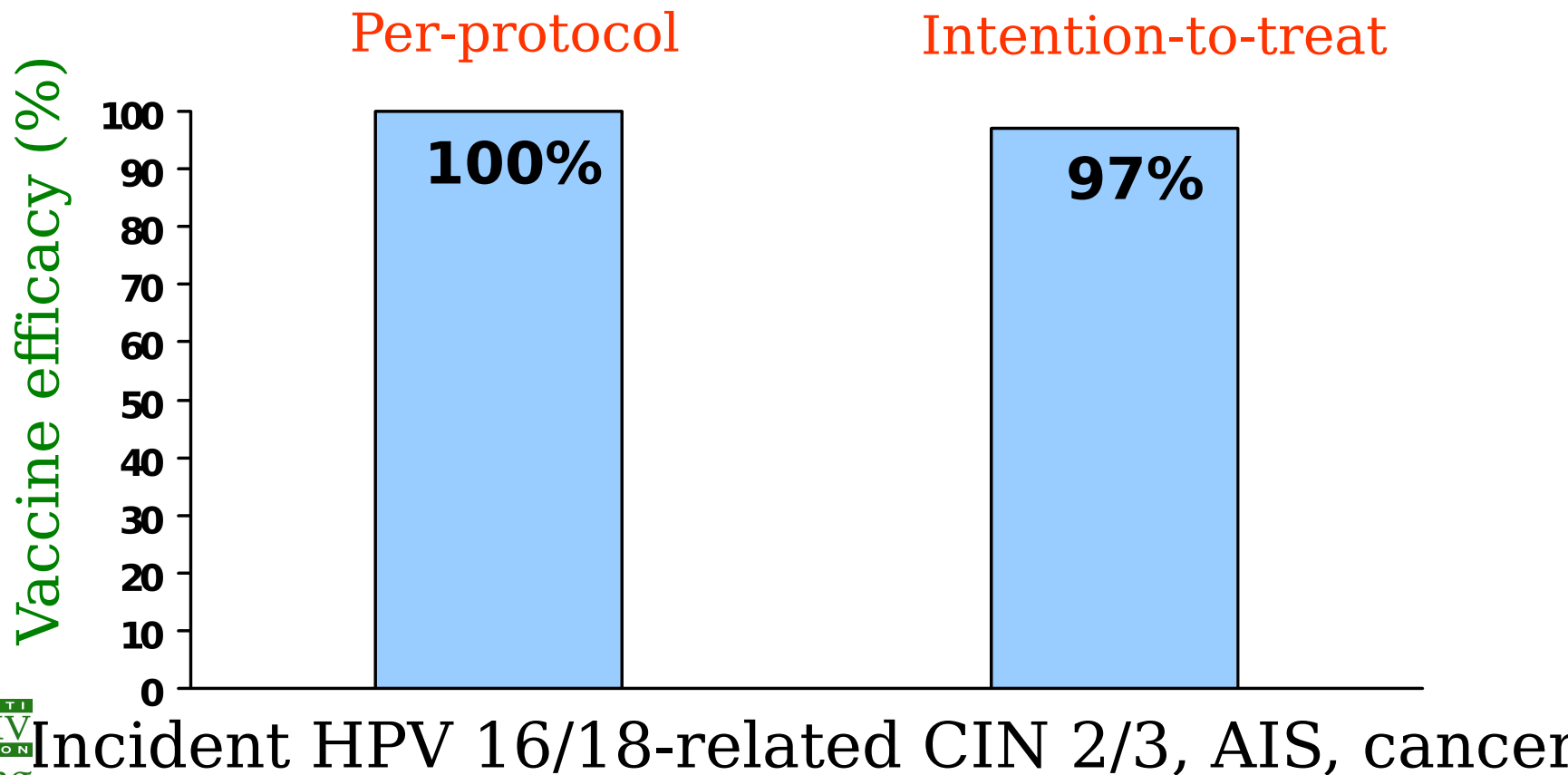
Vaccine-associated AEs	Vaccine (%)	Placebo (%)
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Injection site	86	77
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Systemic	38	33
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Villa et al. *Lancet Oncology* 2005

FUTURE II: HPV-6,11,16,18 Vaccine (N=12,167, 16-23 years)





Licensing by FDA

- Gardasil: FDA approved
 - Indications
 - Prevention of cervical cancer and genital warts caused by HPV 6, 11, 16, and 18 as well as precancerous lesions (CIN, VIN, VaIN), in girls and women 9-26 years of age
 - Given as three IM injections in upper arm over 6 months (0, 2, 6 months)
- Cervarix: GSK expected to submit application 2006



ACIP Recommendations: Gardasil

- Routine vaccination of all 11-12 year-old girls
- Catch-up of 13 to 26-year-old girls and women
- 9-10 year-old girls at provider's discretion
- Can be administered with Tdap, Td, MCV4, HBV
- Not recommended for use in pregnancy, but category B (no evidence of adverse outcomes)
- Contraindicated in those with immediate hypersensitivity to yeast, any vaccine component



Remaining Questions

- Duration of protection at least 5 years – will boosters be needed?
- Efficacy in immunocompromised individuals?
- Efficacy in men?
- Cost-effectiveness in women, men?
- Feasibility of vaccination in developing countries?
- Impact on cervical cancer screening guidelines?
- Impact on behaviors (sexual, screening)?



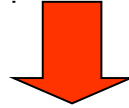
Potential Public Health Benefits

- Prevent cervical cancer
- Decrease racial and ethnic disparities in cervical cancer incidence and mortality
- Prevent other HPV-related diseases
 - Respiratory warts, genital warts, genital cancers, head/neck/digestive system cancers
- Alleviate physical, emotional suffering
- Decrease health care costs

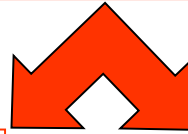


Public Health Impact of HPV Vaccination Will Depend on Uptake

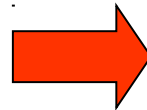
Approval by the FDA



Recommendations by ACIP, professional organizations



Strategies to facilitate
implementation and
uptake



Adoption of
recommendations by
providers, acceptance
by parents



Challenges Related to Uptake

- Poor understanding about HPV, link to cancer
- Getting older children, young teens in for three immunizations over a 6-month period
- Reaching the most vulnerable teens
- Cost: \$360
- Coverage by third-party payors, VFC
- Widespread uptake (without mandates)
- Acceptability of HPV vaccines



Maximizing Vaccine Uptake Health Care Providers

- Brief, practical information about HPV and vaccines
- Guidance re: parental concerns
- Evidence-based interventions that focus on attitudes, endorsement
- Office procedures to maximize vaccination
 - Recall/reminder systems, standing orders
 - Provider auditing, feedback systems
 - Flagging of charts when vaccines due/overdue
 - Vaccinating during sports PEs, urgent care visits



Maximizing Vaccine Uptake Parents and Adolescents

- Information about HPV and vaccines
 - Vaccine safety, efficacy
 - Culturally sensitive
 - Promotes safe sexual behaviors, Pap screening
- Evidence-based interventions that focus on modifiable attitudes, address specific concerns
- Provider recommendation



Maximizing Vaccine Uptake Outside of Office Settings

- Media
 - Print, radio, internet
- Pharmaceutical companies
 - Direct marketing, ensuring adequate vaccine supply
- Public education initiatives
- Vaccine coverage by third-party payors, VFC
- Vaccination in alternative settings (schools?)
- Mandated vaccination?



HPV Therapies: Historic

- Penny – under tape
- Spunk water compress
- Tail hair from a black tomcat
- Coal oil
- Turpentine
- Skunk oil with garlic



HPV Therapies: Historic Modifiers

- Incantations
- Time of night
- Phase of the moon
- Proximity to a cemetery
- Reputation of the therapist



Total Body Condom





If all else fails.....



Human Papilloma Virus

For More Information:
Cincinnati STD/HIV



Prevention Training Center

Toll Free

1-800-459-2820

Fax 1-513-357-7306



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